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File No. IN01156

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Arasappan *et al.*

Serial No.: 09/909,077 Group Art Unit: 1653

Filed: July 19, 2001 Examiner: David Lukton

For: NOVEL IMIDAZOLIDINONES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS

Confirmation No.: 9892

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the office action mailed July 15, 2003. Also enclosed is a Marked-Up Amendment and a Sequence Listing (paper copy and CRF on diskette).

AMENDMENT

(1) Please insert the enclosed "Sequence Listing" after the "Abstract of the Invention".

(2) Please replace the last paragraph of page 67 with the following:

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Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease was performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic

ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates were derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva) (SEQ ID NO: 1), where X = A or P) whose C-terminal carboxyl groups were esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Presented below are the synthesis, characterization and

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(3) Please replace the second paragraph of page 70 with:

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Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27) (SEQ ID NO: 2), Ac-DTEDVVA(Nva)-OH (SEQ ID NO: 3) and Ac-DTEDVVP(Nva)-OH (SEQ ID NO: 4) were determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data were fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m)$, was used to calculate the K_i* value.

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REMARKS

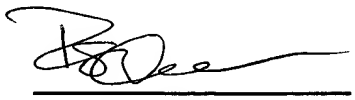
Entry of the foregoing amendment is requested. The amendment adds sequence identifiers next to the peptide sequences in the specification. No new matter was added to the application.

Under 37 C.F.R. § 1.821, the enclosed Sequence Listing lists all peptides in the specification which comprise at least 4 amino acids.

Statement under 37 C.F.R. § 1.825

The content of the attached paper entitled "SEQUENCE LISTING" and of the accompanying identically labeled diskette, specifically the text file therein labeled "seqlist.txt", is the same.

Respectfully submitted,



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